Stress-Evoked Opioid Release Inhibits Pain in Major Depressive Disorder

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Abstract

To determine whether stress-evoked release of endogenous opioids might account for hypoalgesia in major depressive disorder (MDD), the μ-opioid antagonist naltrexone (50 mg) or placebo was administered double-blind to 24 participants with MDD and to 31 non-depressed controls. Eighty minutes later participants completed a painful foot cold pressor test and, after a 5-minute interval, began a 25-minute arithmetic task interspersed with painful electric shocks. Ten minutes later participants completed a second cold pressor test. Negative affect was greater in participants with MDD than in non-depressed controls throughout the experiment, and increased significantly in both groups during mental arithmetic. Before the math task, naltrexone unmasked direct linear relationships between severity of depression, negative affect while resting quietly, and cold-induced pain in participants with MDD. In contrast, facilitatory effects of naltrexone on cold- and shock-induced pain were greatest in controls with the lowest depression scores. Naltrexone strengthened the relationship between negative affect and shock-induced pain during the math task, particularly in the depressed group, and heightened anxiety in both groups toward the end of the task. Thus, μ-opioid activity apparently masked a positive association between negative affect and pain in the most distressed participants. These findings suggest that psychological distress inhibits pain via stress-evoked release of opioid peptides in severe cases of MDD. In addition, tonic endogenous opioid neurotransmission could inhibit depressive symptoms and pain in people with low depression scores.

Keywords: major depressive disorder; naltrexone; stress-induced analgesia; cold pressor; negative affect

Introduction

The incidence of major depressive disorder (MDD) ranges between 30-54% in clinic-based chronic pain patients [4], whereas only about 17% of the general population meet the diagnostic criteria for MDD during their lifetime [8]. In fact, depression is more common in chronic pain patients than in most other chronic medical conditions [4, 19]. While the discomfort, distress, and psychosocial consequences of being in chronic pain undoubtedly promote depression [42], a prior history of depression also heightens vulnerability to chronic pain [31, 45]. Among other possibilities, this might entail neurochemical disturbances (e.g., in serotonin, noradrenaline or opioid neurotransmitters) in affective and pain modulation pathways within the central nervous system.

Patients with MDD rate the intensity of post-operative pain and other painful clinical conditions higher than controls [32, 34]. Surprisingly, however, depressed patients are *less* sensitive than controls to pain induced by standard laboratory stimuli such as contact heat or electrical stimulation [13-15, 33]. The mechanism of this hypoalgesia is uncertain, but could involve stress-induced hypersecretion of beta-endorphins in the bloodstream [5, 12, 22] or, alternatively, heightened activity in cortical or subcortical pathways responsible for stress-induced analgesia [37]. At the cortical level, μ-opioid receptor activity decreases in the rostral anterior cingulate cortex in non-depressed women during induction of sustained sadness but increases in the left inferior temporal cortex of women with MDD, presumably in an effort to suppress emotional responses [30]. At the subcortical level, decreased bioavailability of μ-opioid receptors in the posterior thalamus of MDD patients is associated with raised plasma corticotropin and cortisol levels, both markers of activity in the hypothalamic-pituitary-adrenal axis [30]. The decreased μ-opioid receptor bioavailability is thought to be due to their occupation by opioid

neurotransmitters or to receptor down-regulation. Such mechanisms might explain why morphine fails to suppress cortisol secretion in MDD [49].

The aim of the present study was to investigate the effects of μ-opioid receptor blockade and psychological stress on sensitivity to pain in people with MDD. In a previous study that involved non-depressed participants, the μ-opioid receptor antagonist naltrexone intensified cold-induced pain after stressful mental arithmetic in the most discouraged cases [20], implying that discouragement triggers opioid analgesia [3]. As discouragement (presenting as a sense of helplessness or hopelessness) is one of the key features of depression [24], it was hypothesised that naltrexone would intensify pain more readily in participants diagnosed with MDD than in non-depressed controls. This would support the view that the opioid system is over-active in MDD.

Method

Participants

The study was advertised in local newspapers and on radio, and fliers were distributed in waiting rooms of general practitioners, psychologists and psychiatrists. Respondents were interviewed over the telephone to screen for inclusion and exclusion criteria, and the Structured Clinical Interview for DSM-IV Axis I Disorders – Clinician Version [18] was administered to establish the diagnosis of MDD. Eleven men and 13 women aged between 17 and 57 years met the criteria for MDD. Another 14 men and 17 women aged between 18 and 57 years who had no personal or family history of psychiatric illness were recruited as controls. Depressed participants reported significantly higher levels of anxiety, stress and depression than non-depressed controls on the State-Trait Anxiety Inventory, Form Y (STAI) [44], Depression, Anxiety, and Stress Scales (DASS) [36], and the Beck Depression Inventory II (BDI) [6] (Table 1). In

comparison to the general adult population, controls reported lower than average levels of state anxiety (women 39th mean percentile rank; men 44th mean percentile rank) and trait anxiety (women 42nd mean percentile rank; men 43rd mean percentile rank), and levels of depression and stress were within the normal range. Conversely, depressed participants reported moderate to severe symptoms of state and trait anxiety, matching levels in the top 2-5% of the general population [44]. All participants reported that they were in good health.

Exclusion criteria included psychotic disorders, alcohol and/or other substance use disorders, benzodiazepines, DSM-IV Axis II disorders, cigarette smoking, chronic pain conditions or headache (all identified during the structured clinical telephone interview). In addition, respondents currently taking hypericum perforatum (St John's Wort) or antidepressant medication were excluded. Five participants had taken selective serotonin reuptake inhibitors in the past but had ceased taking these drugs five weeks to six months (median four months) before their recruitment into the study. Participants reduced their alcohol intake for one week prior to testing, and refrained from alcoholic or caffeinated beverages for 12 hours before the experiment. They also refrained from food for two hours before the experiment. None of the participants used opiates regularly or had ever taken naltrexone.

Participants provided informed consent for the procedures which were approved by the Murdoch University Human Research Ethics Committee. Two depressed participants withdrew from the experiment during the math task and one control withdrew because of an adverse reaction to naltrexone (vertigo). Participants received $20 for their participation.

Procedures

Design overview. The experiment was carried out in a laboratory maintained at 22 ± 2°C. The participants were randomly assigned to either a naltrexone or placebo condition. An identical capsule containing a 50 mg caplet of naltrexone or a sugar pill was administered double-blind. This dose of naltrexone blocks the subjective and objective effects of intravenous opioid challenge [11, 21], and would be expected to block effects of endogenous opioid release. When asked after the experiment whether they thought that they had taken naltrexone, participants guessed correctly at a rate no greater than chance. In the depressed group, four men and six women took naltrexone, and another seven men and seven women took the placebo. In the control group, six men and eight women took naltrexone, and another eight men and nine women took the placebo. Eighty minutes later, after the naltrexone had been absorbed [21], participants completed a cold pressor test and, after a 5-minute interval, began a 25-minute arithmetic task. Participants completed a second cold pressor test ten minutes after the arithmetic task. Naltrexone has a half-life of approximately four hours [11].

Dependent variables. Prior to drug absorption, an hour later and again after the math task, participants rated anxiety, discouragement, anger and filler items (confusion, sluggishness and liveliness) on separate 100 mm visual analogue scales ranging from "not at all" to "extremely". The participants were instructed to rate how they felt right now. Subjects rated their mood using the same scales at intervals of 5-7 minutes during the arithmetic task, starting 1.5 minutes into the task. During the cold pressor test participants rated pain and unpleasantness at 30-second intervals using two 0-10 point verbal rating scales until the pain became intolerable – at which point a final rating was made (0 corresponded to 'no pain' or 'not unpleasant at all' and 10 to 'pain as bad as it

could get' or 'as unpleasant as it could get'). In addition, the intensity and unpleasantness of seven painful electric shocks administered during the math task were rated on 100 mm visual analogue scales ranging from "no pain" or "not unpleasant at all" to "pain as bad as it could get" or "as unpleasant as it could get".

Cold pressor test. Participants immersed their non-dominant foot to the top of the lateral malleolus in 37°C water for three minutes to standardise foot temperature, then placed their foot in 2°C ice-water for as long as they could tolerate or until four minutes had elapsed. A small aquarium pump circulated the ice-water to prevent pockets of warm water developing around the foot.

Math task. Addition and subtraction items varied across five levels of difficulty, and the difficulty of the problems was adjusted automatically to ensure a 75% failure rate across the 25 minutes of the task [20]. At the outset of the task subjects were told that the number of shocks that they would receive would depend on their performance. However, no such contingency existed and all participants received an identical number of shocks at similar stages throughout the task. Each math question appeared in yellow 2 cm high numbers in the middle of a black computer screen. To increase the difficulty of the task, subjects used their non-dominant hand to type in their answers using the row of numbers at the top of a computer keyboard (and not the number-pad). Once a problem was completed or time had elapsed for that question, feedback such as 'CORRECT' (green), 'INCORRECT' (red) or 'TOO SLOW' (purple) appeared on the computer screen. Either a pleasant 3-note jingle (correct response) or an aversive loud beep (too slow or incorrect response) sounded for one second.

Electric shocks. Seven 15 mA shocks of 25 milliseconds duration were delivered at irregular intervals throughout the math task to prevent subjects from anticipating their

occurrence. Each pulse was delivered by an SD9 Grass Square Pulse stimulator and constant current unit via 1 cm^2 silver/silver chloride surface electrodes filled with water-soluble electrode gel and attached 2 cm apart over the right lateral sural nerve behind the lateral malleolus. The skin was slightly abraded with a pumice stone and degreased with an alcohol swab to reduce skin impedance below 5 KΩ. The math task was suspended after each shock whilst subjects gave pain intensity and unpleasantness ratings.

Data analysis

Mood ratings. Changes in anxiety, discouragement and anger over the course of the experiment were investigated in Group (depressed, control) x Drug (natrexone, placebo) x Time (before drug administration, 60 minutes after drug administration, five times during the math task, and shortly after the math task) analyses of variance. The multivariate solution was employed for repeated measures factors with more than two levels. Significant effects that included Time were investigated in planned contrasts between consecutive time points.

Cold-induced pain. Tolerance scores derived from the duration of foot immersion were log-transformed to reduce the distribution skew created by participants who tolerated the cold pressor test for the entire four-minute period. These log-transformed scores, and mean ratings of the intensity and unpleasantness of pain, were investigated in Group x Drug analyses of variance. The relationship between cold-induced pain, depression severity and prior mood was investigated with Pearson's correlation coefficient. Differences in the relationship between the naltrexone and placebo conditions were investigated in hierarchical multiple linear regression analyses, calculated separately for depressed and non-depressed participants because of substantial differences in mood between the two groups. In each regression model, the Drug condition (naltrexone or

placebo) was dummy-coded and entered in the first step. Mood or depression severity was also entered in the first step, and the interaction term (the product of Drug and Mood or Depression Severity) was entered in the second step. The Drug x Mood/Depression Severity interaction tested whether naltrexone altered the relationship between pain ratings and mood (as might be expected if stress-evoked opioid release inhibits pain).

Shock-induced pain. Ratings of the intensity and unpleasantness of shock-induced pain (averaged over the seven shocks) were investigated in analyses of variance with factors of Group and Drug. The relationship between shock-induced pain and mood/depression severity ratings during the math task was investigated with Pearson's correlation coefficient and in hierarchical multiple linear regression analyses, as described above.

The criterion of statistical significance was $p<0.05$. Data are reported as the mean $\pm$ standard error.

Results

Mood ratings

As shown in Figure 1, negative affect was greater in depressed participants than controls throughout the experiment [for anxiety, $F(1,50) = 6.31$, $p<0.05$; for discouragement, $F(1,50) = 17.6$, $p<0.001$; for anger, $F(1,50) = 10.2$, $p<0.01$].

Anxiety ratings differed across the course of the experiment [main effect for Time, $F(7,44) = 16.7$, $p<0.001$]. In particular, anxiety decreased after drug administration ($p<0.05$) but then increased rapidly during the math task (difference between pre-math anxiety and first measure during math, $p<0.001$) (Figure 1A-B). Both in depressed and non-depressed participants, ratings decreased during the second half of the task in the placebo condition but continued to increase in the naltrexone condition [Time x Drug,

$F(7,44) = 2.96$, $p<0.05$] (Figure 1A-B). Investigation of this interaction indicated that anxiety decreased in the placebo condition between the third and fourth measurement points (approximately 15 minutes into the task) but continued to increase in the naltrexone condition [Time (third to fourth measurement point) x Drug $F(1,50) = 15.7$, $p<0.001$]. Anxiety decreased in all groups after the math task (difference between final measure during math and the post-math measure, $p<0.001$).

Discouragement and anger also differed across the course of the experiment [for discouragement, $F(7,44) = 12.9$, $p<0.001$, for anger, $F(7,44) = 8.54$, $p<0.001$] (Figure 1C-F). In particular, both discouragement and anger increased rapidly during the math task (difference between pre-math anxiety and first measure during math, $p<0.001$) and remained high until after the task had finished (difference between the final measure during math and the post-math measure, $p<0.05$ for discouragement and $p<0.01$ for anger). Naltrexone did not influence ratings of discouragement or anger in depressed or non-depressed participants.

Cold-induced pain

Both before and after the math task, approximately 40% of participants tolerated the cold pressor test for the entire four-minute period. These participants were spread fairly evenly across the naltrexone and placebo conditions in the depressed and control groups (Table 2). The cold pressor test was rated as moderately to intensely painful and unpleasant: intensity ratings averaged 7.5 $\pm$ 0.3 and unpleasantness ratings averaged 7.8 $\pm$ 0.3 on 0-10 scales. In the group as a whole, neither pain tolerance nor pain ratings differed between the naltrexone and placebo conditions, or between depressed participants and controls, before or after the math task (none of the F ratios that included these effects were statistically significant).

In depressed participants who took naltrexone, depression severity and negative affect before the first cold pressor test was greatest in those who subsequently reported most cold-induced pain (Table 3). However, this relationship moved in the opposite direction in depressed patients who took the placebo. Hierarchical multiple linear regression analyses confirmed that naltrexone reversed the relationship between negative affect/depression severity and pain in depressed participants during the first cold pressor test (Table 3). Naltrexone also reversed the association between depression severity and pain unpleasantness after the math task (Table 4), but did not alter the relationship between pain and anxiety, discouragement or anger.

Naltrexone did not influence the association between negative affect and pain in controls, either before or after the math task (Tables 3 and 4). Curiously, however, naltrexone unmasked a negative association between pain ratings and depression severity scores in controls (Tables 3 and 4).

Shock-induced pain

Electric shocks administered during the math task were rated as moderately painful. Neither ratings of pain intensity nor unpleasantness differed significantly between depressed participants and controls, or between the naltrexone and placebo conditions.

In the naltrexone condition, the intensity and unpleasantness of shock-induced pain was greatest in subjects who reported most negative affect (Table 5). In depressed participants, the relationship between pain ratings and negative affect was stronger in the naltrexone condition than the placebo condition (Table 5). Pain ratings were unrelated to depression severity scores in the MDD group, but were negatively associated with depression severity scores in controls administered naltrexone (Table 5).

Discussion

The main finding of this study was that the μ-opioid receptor antagonist naltrexone strengthened the relationship between negative affect and pain, particularly in the MDD group. This finding suggests that psychological stress triggered the release of endogenous opioid peptides in the most distressed participants, and that μ-opioid activity masked a direct linear relationship between negative affect and pain.

Stress-induced analgesia

Opioid analgesia has been identified in a diverse range of animal models, characterized by lack of control over aversive stimuli such as cold-water immersion, electric shocks, and centrifugal rotation [1, 41]. In human research, μ-opioid receptor blockade antagonized stress-induced analgesia evoked by noxious electric shocks [47, 48], immersion of a limb in ice-water [28, 40], the perception of failure on a difficult cognitive task [2, 3, 20], a combat video shown to Vietnam veterans with post-traumatic stress disorder [38], and a first-time parachute jump [27]. Effects of μ-opioid receptor blockade on experimental pain are more variable [16, 23, 40], possibly because of individual differences in sensitivity to or release of opioid peptides. For example, naloxone augments shock-induced pain and cortical evoked potentials in pain-tolerant people, but inhibits pain and cortical evoked potentials in pain-sensitive people [10]. We recently reported that μ-opioid receptor blockade facilitated pain induced by repeated immersions of a hand in ice-water in pain-tolerant subjects, but had no effect on pain induced by the first, less stressful, immersion [40]. In the present study, naltrexone failed to augment pain induced by electric shocks or single ice-water immersions in the group as a whole. Thus, psychological stress may trigger endogenous opioid release more readily than transient painful stimulation.

We previously investigated the effect of naltrexone on cold-induced pain in non-depressed people before and after stressful mental arithmetic [20]. To heighten negative affect, participants received noxious electric shocks at irregular intervals throughout the math task. Within the naltrexone condition, cold-induced pain and unpleasantness increased after the math task in line with ratings of discouragement. This relationship was absent in the placebo condition, implying that opioid release inhibited cold-induced pain in the most discouraged cases. In the present study, a similar protocol was employed to investigate effects of MDD on stress-induced opioid analgesia. In contrast to our previous report [20], naltrexone unmasked a positive association between negative affect and cold-induced pain *before* the math task in depressed participants; moreover, in the naltrexone condition, both cold-induced pain and unpleasantness increased in line with depression severity. These relationships were absent in the placebo condition, implying that psychological distress mobilized the opioid system in MDD. Thus, our findings suggest that chronic stress-induced activation of the opioid system inhibited cold-induced pain in severely depressed participants. In emotionally-neutral states, the bioavailability of μ-opioid receptors in the posterior thalamus is lower in women with MDD than in non-depressed controls, consistent with chronic over-activity of the opioid system in MDD [30]. Bioavailability of μ-opioid receptors decreases in this part of the brain during painful stimulation [7, 50], presumably due to pain-induced release of endogenous opioids.

During stressful mental arithmetic, naltrexone strengthened an association between negative affect and shock-induced pain, particularly in the MDD group. Opioid activity increases in the subamygdalar-left inferior temporal cortex of depressed patients during sustained sadness, and increases in the anterior cingulate region of patients who

fail to respond to antidepressant medication [30]. Thus, the μ-opioid system may be over-active in severely affected MDD patients, not only at rest but also during emotional challenges.

After the math task, naltrexone strengthened an association between pain unpleasantness and severity of depression in the MDD group, suggesting that opioid analgesia was greatest in the most severely depressed cases. Surprisingly, however, naltrexone-hyperalgesia was unrelated to the intensity of negative affect. The reason for this discrepancy is unclear, but may be due to the development of non-opioid analgesia during stressful mental arithmetic. Non-opioid analgesic mechanisms appear to be active during stressful experiences until the outcome is no longer easily controlled; this loss of control then augments endogenous μ-opioid neurotransmission [2, 29].

Curiously, naltrexone-hyperalgesia was greatest in controls with the *lowest* depression severity scores (contrary to participants with MDD). Opioid activity decreases in the rostral anterior cingulate region of non-depressed controls during sustained sadness, in association with heightened negative affect [30]. Thus, in the absence of depression, sadness may be associated with a reduction in normal, background opioid release in a region of the brain that regulates affective responses. The present findings suggest that naltrexone blocked an analgesic effect of tonic opioid release in non-depressed controls with few or no depressive symptoms. Importantly, naltrexone had little influence on the mood-pain relationship in this group, implying that heightened tonic μ-opioid neurotransmission was associated more closely with lack of depressive symptoms than with negative affect.

<u>Effect of naltrexone on mood</u>

Negative affect was greater in depressed than non-depressed participants throughout the study, as was the unpleasantness of shock-induced pain. Although increments in negative affect were similar in both groups during the math task, naltrexone blocked decreases in anxiety toward the end of the task. Thus, stress-induced opioid release apparently suppressed anxiety both in MDD participants and non-depressed controls. Functional neuroimaging studies suggest that the endogenous opioid system has an anxiolytic role in regions of the temporal lobe that project to the amygdala [35], and suppresses affective states such as sadness [30, 51].

Negative affect during stressful mental arithmetic increased in line with the intensity and unpleasantness of shock-induced pain, particularly in the naltrexone condition. The positive association between negative affect and pain could reflect several mechanisms, including hypervigilance to pain, muscular reactivity, autonomic arousal, or misattribution of arousal in distressed participants [26]. Alternatively, the pain provoked by the electric shocks may have enhanced negative affect. Animal studies have implicated activation of the limbic system, a deficit in central serotonergic neurotransmission, dysfunction of the hypothalamic-pituitary-adrenal axis, and hypofunction of supraspinal μ-opioid receptors in various models of stress-induced hyperalgesia [25]. Whatever the mechanism, the present findings indicate that endogenous opioids masked the relationship between negative affect and pain, particularly in the MDD group.

Limitations

The rigorous inclusion and exclusion criteria used to select MDD participants and controls places limits on how far the present findings might generalize to their respective populations. Many potential recruits with MDD were excluded because they took drugs

that might affect μ-opioid neurotransmission (antidepressants, nicotine, psychotropic agents or pain medication). Controls had to be free of psychiatric illness, both personally and within their immediate family. The use of these selection criteria may account for discrepancies between the present findings and those reported previously. For example, we previously found evidence of opioid analgesia in discouraged participants after stressful mental arithmetic [20]. In contrast, opioid analgesia after the math task was unrelated to discouragement in the present study, perhaps due to a restricted range of affect within homogenous groups of participants.

In a second important discrepancy, naltrexone enhanced anxiety during the math task in the present study. The present sample of participants was recruited from the community, and might have felt more threatened by task demands (thereby activating the opioid system more strongly to counteract anxiety) than the previous university-based sample [20].

We asked participants to rate discouragement rather than sadness because loss of control (akin to a sense of helplessness or hopelessness) appears to be important both in depression [24] and in stress-induced opioid analgesia [2, 3]. In retrospect, however, it would have been interesting to measure sadness in addition to discouragement because melancholia is a major feature of depression.

Finally, opioid analgesia was greater in women than men in our previous study [20], possibly because women became more discouraged than men during the math task. The sample recruited for the present study was not large enough to investigate sex differences in opioid analgesia within the MDD population. However, sex differences may be important because women are more sensitive to pain than men [17, 46] due, in part, to modulatory effects of oestrogen on subcortical opioid neurotransmission [43].

Conclusions

Lautenbacher et al. [33] reported that μ-opioid receptor blockade had no consistent effect on heat pain thresholds in depressed patients. Similarly, in the present study, naltrexone had no consistent effect on pain intensity in the MDD group as a whole, either before, during or after psychological stress. Nevertheless, naltrexone strengthened the relationship between negative affect and cold- and shock-induced pain, particularly in the MDD group, consistent with heightened μ-opioid neurotransmission and opioid analgesia in the most distressed cases. These findings support the view that the opioid system, which forms an interface between physical and emotional stress regulation [39], is chronically over-active in the most severe cases of MDD [30]. Further studies are required to determine whether this over-activity promotes opioid tolerance, a factor implicated in the development of chronic pain [9].

Our findings also suggest that high tonic μ-opioid neurotransmission inhibited pain in controls with few or no symptoms of depression. If so, high tonic levels of opioid activity might decrease vulnerability to depressive symptomatology.

Acknowledgements

The authors have no conflict of interest with the contents of this paper.

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Table 1: Anxiety, depression and stress in depressed participants and controls

	Depressed (N = 24)	**Controls (N = 31)**	
	Mean ± SD	**Mean ± SD**	***t-test***
Age (years)	35.3 ± 12.0	36.3 ± 13.2	.29
STAI			
State anxiety	56.9 ± 13.3	31.6 ± 8.3	8.77*
Trait anxiety	58.2 ± 10.9	31.6 ± 8.3	10.30*
DASS			
Depression scale	23.7 ± 10.9	3.0 ± 4.8	9.49*
Anxiety scale	14.0 ± 10.8	1.8 ± 2.2	6.11*
Stress scale	25.2 ± 10.7	6.5 ± 5.4	8.40*
BDI-II			
Depression	27.6 ± 12.6	3.6 ± 3.6	10.08*

Note. *p<.001

Table 2: Number of participants who tolerated the cold pressor test for the full four minutes

	Depressed	**Controls**
Before math		
Placebo condition	5/14 (38%)	7/17 (41%)
Naltrexone condition	3/10 (30%)	6/14 (43%)
After math		
Placebo condition	6/14 (43%)	8/17 (47%)
Naltrexone condition	2/10 (20%)	6/14 (43%)

Note: the proportion of participants who tolerated the cold pressor test for the full four minutes did not differ significantly between the placebo or naltrexone conditions in depressed participants or controls, either before or after the math task.

Table 3: Association between mood and cold-induced pain before the math task

	Major Depressive Disorder			Controls		
	Correlations		F(1,20)^	Correlations		F(1,27)^
	Placebo (N = 14)	Naltrexone (N = 10)		Placebo (N = 17)	Naltrexone (N = 14)	
Pain Intensity						
Depression severity #	-.41	**.80*** **	**6.02***	.42	**-.54***	**6.59***
Anxiety	-.38	**.67***	**4.64***	.06	-.18	.32
Discouragement	-.40	**.63***	**4.69***	.06	-.09	.13
Anger	-.33	.55	3.01	.06	.02	.03
Unpleasantness						
Depression severity #	-.45	**.63***	**5.73***	.37	-.44	**4.80***
Anxiety	-.39	.61	**4.78***	.04	-.13	.17
Discouragement	-.40	.57	**4.61***	.04	-.04	.05
Anger	-.34	.44	2.79	.04	-.01	.02
Pain tolerance						
Depression severity #	.00	-.49	1.37	-.17	.23	1.21
Anxiety	-.22	-.46	.15	-.03	.28	1.09
Discouragement	-.21	-.60	.55	.31	-.08	.90
Anger	-.29	-.56	.34	.31	-.18	1.89

*p<.05; *** p<.001

Scores on the Beck Depression Index were used as an index of depression severity. These scores ranged between 4 and 49 in the MDD group and between 0 and 13 in controls.

^ The Drug x Depression Severity/negative affect interaction in hierarchical multiple linear regression analyses, which tests whether correlations differ between the placebo and naltrexone conditions.

Table 4: Association between mood and cold-induced pain after the math task

	Major Depressive Disorder			Controls		
	Correlations		F(1,20)^	Correlations		F(1,27)^
	Placebo (N = 14)	Naltrexone (N = 10)		Placebo (N = 17)	Naltrexone (N = 14)	
Pain Intensity						
Depression severity #	-.41	.45	3.38	.36	**-.55***	**6.48***
Anxiety	-.07	.11	.12	.04	.38	.83
Discouragement	-.02	.28	.19	-.08	.34	1.15
Anger	.06	.41	.12	-.16	.25	1.15
Unpleasantness						
Depression severity #	-.46	.50	**4.39***	.37	-.44	**4.82***
Anxiety	-.06	.22	,22	.17	.35	.20
Discouragement	-.05	.43	.58	.10	.31	.23
Anger	-.03	.49	.53	.02	.32	.47
Pain tolerance						
Depression severity #	.04	-.41	1.17	-.28	.31	2.50
Anxiety	-.36	-.41	.02	-.21	-.09	.03
Discouragement	-.28	-.54	.80	-.16	-.28	.37
Anger	-.18	**-.72***	1.68	-.11	-.01	.00

*p<.05

Scores on the Beck Depression Index were used as an index of depression severity.

^ The Drug x Depression Severity/negative affect interaction in hierarchical multiple linear regression analyses, which tests whether correlations differ between the placebo and naltrexone conditions.

Table 5: Association between shock-induced pain and mood during the math task

	Major Depressive Disorder			Controls		
	Correlations		F(1,20)^	Correlations		F(1,27)^
	Placebo (N = 14)	Naltrexone (N = 10)		Placebo (N = 17)	Naltrexone (N = 14)	
Pain Intensity						
Depression severity [#]	-.27	.09	.52	.21	**-.54***	**5.88***
Anxiety	.10	**.80****	**5.98***	.46	**.79*****	2.43
Discouragement	-.03	**.78***	**7.72***	.14	**.64***	4.14
Anger	.03	.63	2.78	.34	.38	.43
Unpleasantness						
Depression severity [#]	-.18	-.05	.03	.02	-.45	2.35
Anxiety	.18	**.84****	**7.74***	**.58***	**.52**	.00
Discouragement	.13	**.90*****	**12.6****	.30	**.65***	2.40
Anger	.15	**.78***	**4.80***	.39	.07	.36

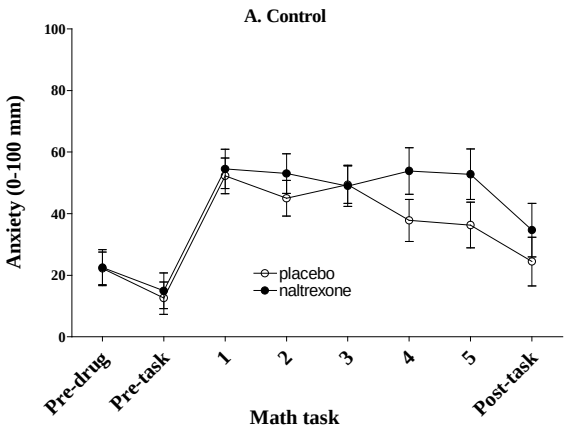
*p<.05; **p<.01; ***p <.001

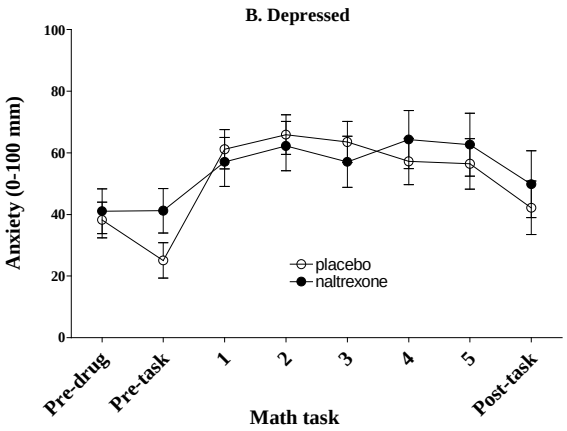
[#] Scores on the Beck Depression Index were used as an index of depression severity.

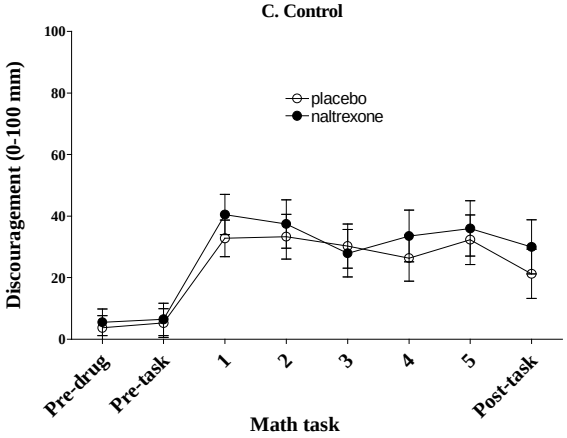
^ The Drug x Depression Severity/negative affect interaction in hierarchical multiple linear regression analyses, which tests whether correlations differ between the placebo and naltrexone conditions.

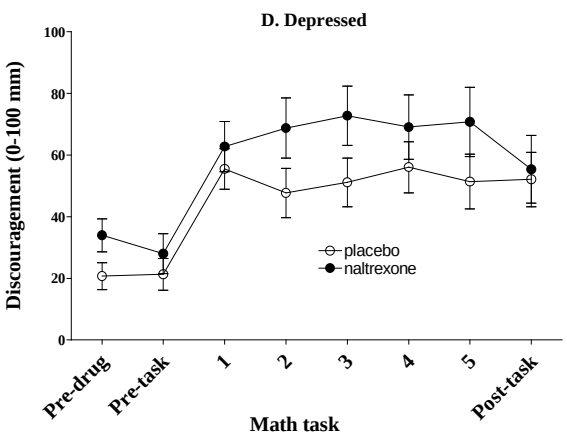
Figure legend

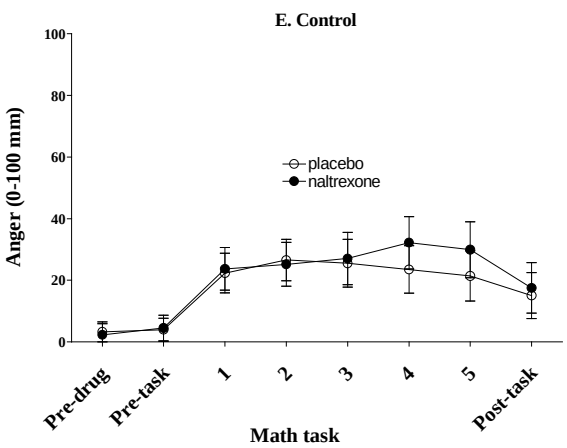
Figure 1. Change in mood ratings (± S.E.) over the course of the experiment in the naltrexone condition (filled circles) and placebo condition (open circles).

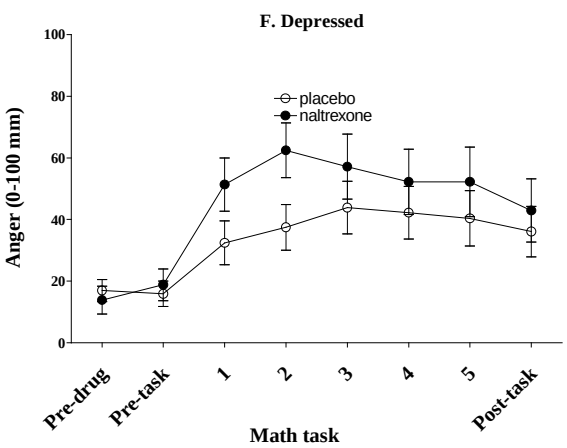

A. Control
Anxiety (0-100 mm)
placebo
naltrexone
Pre-drug
Pre-task
1
2
3
4
5
Post-task
Math task


B. Depressed
Anxiety (0-100 mm)
placebo
naltrexone
Pre-drug
Pre-task
1
2
3
4
5
Post-task
Math task


C. Control
Discouragement (0-100 mm)
placebo
naltrexone
Pre-drug
Pre-task
1
2
3
4
5
Post-task
Math task


D. Depressed
Discouragement (0-100 mm)
placebo
naltrexone
Pre-drug
Pre-task
1
2
3
4
5
Post-task
Math task


E. Control
Anger (0-100 mm)
placebo
naltrexone
Pre-drug
Pre-task
1
2
3
4
5
Post-task
Math task


F. Depressed
Anger (0-100 mm)
placebo
naltrexone
Pre-drug
Pre-task
1
2
3
4
5
Post-task
Math task